Neurocrit Care
https://doi.org/10.1007/s12028-025-02376-0

NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

The Association between Hourly Systolic Blood Pressure Variability and Outcomes in Patients with Intracerebral Hemorrhage is Time-Dependent: Post-hoc Analysis of the ATACH-2 Trial

Adnan I. Qureshi[1,2*], William Baskett[3], Joao A. Gomes[4], Pashmeen Lakhani[1], Alejandro A. Rabinstein[5], David Z. Rose[6], Jose I. Suarez[7], Thorsten Steiner[8,9] and Chi-Ren Shyu[3]

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Abstract

Background: Systolic blood pressure (SBP) variability has been associated with an increase in rates of death or disability in patients with intracerebral hemorrhage (ICH). We analyzed data from the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-2 trial to determine whether the association between SBP variability and death or disability at 90 days is dependent on the time from randomization.

Methods: The difference between maximum and minimum SBP (hourly SBP range) for the first 24 h after enrollment was used to calculate the hourly SBP variability. The effect of hourly SBP variability was evaluated in logistic regression models on: (1) death or disability (modified Rankin scale score of 4–6 at 90 days), (2) hematoma expansion (increase of > 33% in volume on the computed tomography scan obtained at 24 h) within 24 h, (3) neurological deterioration within 24 h, and (4) acute kidney injury within 72 h after enrollment. We adjusted for age, baseline Glasgow Coma Scale score, intraventricular hemorrhage, hematoma volume, and maximum SBP values for each time window.

Results: A total of 961 patients (mean age ± standard deviation [SD], 62 ± 13 years; 61.9% were men) who were enrolled at a mean ± SD time of 184 ± 56 min from symptom onset were analyzed. The mean ± SD hourly SBP variability was 15.6 ± 16 mm Hg. The hourly SBP variability became significantly lower with increasing time intervals from randomization (ranging from 41.8 ± 23.3 at hour 1 to 12.4 ± 14.0 at hour 24, $P < 0.0001$). SBP variability at five hours ($P = 0.014$) and six hours ($P = 0.014$) after enrollment was significantly associated with death or disability at 90 days, with positive but not statistically significant associations observed at all other points up to eight hours after randomization. Risk of neurological deterioration within 24 h was highly associated with SBP variability, with the largest association observed between one ($P < 0.001$) and five ($P < 0.001$) hours following randomization, with significant associations observed up to 22 h following randomization. Risk of hematoma expansion was associated with SBP variability between three ($P = 0.015$) and eight ($P = 0.002$) hours after randomization. Statistically significant associations between SPB variability and risk of acute kidney injury were not observed.

*Correspondence: qureshai@gmail.com
[1] Zeenat Qureshi Stroke Institute, Columbia, MO, USA
Full list of author information is available at the end of the article

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Conclusions: Reduced SBP variability within the first eight hours following randomization appears most impactful on both short-term and long-term outcomes in patients with ICH, and the first eight hours may represent a time window for future interventions directed at reducing SBP variability in patients with ICH.

Keywords: Systolic blood pressure, Intracerebral hemorrhage, Death or disability, Time-dependent, Neurological deterioration

Introduction

Recent studies have highlighted the importance of blood pressure (BP) variability in the acute phase of intracerebral hemorrhage (ICH) [1–4]. An analysis of the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) trial demonstrated that the standard deviation (SD), coefficient of variation, and successive variation of BP recorded by paramedics in the field and during the first 24 h of the hospital course in patients with ICH were associated with death or disability at three months. Another analysis of the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI)-ICH study cohort found that the SD of systolic BP (SBP) in the first 24 h was associated with neurological deterioration, and successive variation of the SD of SBP in the first 24 h was associated with death or disability at three months [1]. Another analysis of the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-2 trial found that SBP variability in the first 24 h was associated with death or disability at 90 days [3]. An analysis of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT)-2 found that the SD of SBP in the first 24 h had a significant linear association with death or major disability at 90 days [2]. In a pooled analysis of the INTERACT-2 and ATACH-2 trial, SBP variability (the SD of the same measures between 1 and 24 h) was significantly associated with death within 90 days and improved outcomes were associated with reduced SBP variability [4]. We performed this study to analyze the effect of hourly SBP variability on various outcomes in patients with ICH and whether the effect was time-dependent or magnitude-dependent.

Methods

Study Design

The ATACH-2 trial was a randomized multinational trial designed to determine the efficacy of intensive SBP reduction initiated within 4.5 h of symptom onset in study participants with spontaneous supratentorial ICH and SBP ≥ 180 mm Hg [5, 6]. Briefly, study participants with a Glasgow Coma Scale (GCS) score of ≥ 5 at the time of emergency department arrival and an intraparenchymal hematoma of < 60 mm^3 on the initial computed tomography (CT) scan were randomized. The goal of treatment was to reduce within two hours of randomization and maintain through 24 h each study participant's SBP to 140–179 mm Hg in the standard treatment group and 110–139 mm Hg in the intensive treatment group.

Intervention

After randomization, an intravenous (IV) nicardipine infusion was initiated at 5 mg/h and then increased by 2.5 mg/h every 15 min as needed, up to a maximum of 15 mg/h. Once the target SBP level was reached, the infusion rate was adjusted by 1 to 2.5 mg/h to maintain SBP in the specified range. If the SBP fell below the target value, the IV nicardipine was reduced by 2.5 mg/h every 15 min until the infusion was discontinued. Infusion was not restarted unless the SBP was above 180 mm Hg or 140 mm Hg for the standard and intensive treatment groups, respectively. If the SBP was greater than the target despite infusion of the maximum nicardipine dose for 30 min, a prespecified second agent, IV labetalol (5–20 mg IV bolus every 15 min), was used for another hour, or diltiazem (initial infusion rate of 5 mg/h up to 15 mg/h) or uradipil (12.5 mg every 15 min to a maximum dose of 50 mg) was used in countries where labetalol was not available.

BP Measurements

SBP measurements were acquired every five minutes for the first 15 min after initiation of the nicardipine infusion, followed by every 15 min for the remainder of the first hour or every five minutes if the dose was being adjusted. The SBP was measured at least every 30 min while nicardipine was administered or more frequently if prominent SBP changes were observed, as determined by the treating physician.

Data Collection

The maximum and minimum SBP values for each hour were collected for the first 24 h following randomization. A noncontrast head CT scan was performed at baseline and 24 h after initiation of treatment and analyzed by a reader who was anonymized to the treatment assignment, clinical findings, and time points of image acquisition. The parenchymal hematoma volume was measured using automated delineation (with manual correction) by computer software on each slice containing the

hematoma. A complete chemistry panel was performed at baseline and at 24, 48, and 72 h. Adverse events were ascertained only within the first five days or upon discharge (whichever came first). The post-discharge follow-up included telephone contact at 30 days and in-person clinical evaluation at 90 days after randomization. The telephone interview by the site staff collected information on serious adverse events and deaths. The 90-day disability assessments using the modified Rankin scale (mRS) were conducted by a qualified investigator who did not participate in the randomization, treatment, or in-hospital clinical management of the study participant.

Statistical Analysis

The study participants were grouped based on achieved SBP, regardless of randomized allocation. The difference between maximum and minimum SBP (hourly SBP range) was used to calculate the hourly SBP variability. The dichotomized end points of interest included the following: (1) patients with good functional outcome (mRS score of 0–3 at 90 days) versus those with death or disability (mRS score of 4–6 at 90 days after enrollment), (2) patients with hematoma expansion (increase of > 33% in volume on the CT scan obtained at 24 h after enrollment compared with the baseline scan) within 24 h versus those without hematoma expansion, (3) patients with neurological deterioration within 24 h (defined as a decrease from baseline of ≥ 2 points on the GCS or an increase of ≥ 4 points on the National Institutes of Health Stroke Scale score that was not related to sedation/hypnotic use and was sustained for at least 8 h within 24 h) after enrollment versus those without neurological deterioration, and (4) patients with acute kidney injury (AKI) within 72 h after enrollment (increase in serum creatinine levels from baseline, ≥ 0.3 mg/dL) versus those without AKI. The hourly SBP variability was plotted for each of the aforementioned dichotomized end points. A multivariate (logistic regression) analysis was performed using hourly SBP variability as the predictor, with each of the aforementioned dichotomized end points as the dependent variable. Other potential confounders included age, baseline GCS score, intraventricular hemorrhage, hematoma volume at baseline, and maximum SBP values for each time window (one logistic regression model for each hour, resulting in 24 models for each outcome). We could not use minimum SBP because of collinearity causing numerical instability in the model. We performed an exploratory analysis after dividing the magnitude of variability for each hour into four quartiles and determined the relationship between quartiles of increasing magnitude of variability and death or disability and other outcomes at 90 days.

Results

A total of 961 patients (mean age ± SD, 62 ± 13 years; 61.9% were men) were analyzed. The patients were randomized at a mean ± SD time of 184 ± 56 min from symptom onset. The mean ± SD hourly SBP variability was 15.6 ± 16 mm Hg. The median (range) hourly SBP variability was 11 mm Hg (interquartile range of 5–21 mm Hg). The hourly SBP variability was significantly higher in patients who were randomized to standard SBP reduction compared with those randomized to intensive SBP reduction (see Fig. 1). The hourly SBP variability became significantly lower with increasing time intervals from randomization (ranging from 41.8 ± 23.3 at hour 1 to 12.4 ± 14.0 at hour 24, $P < 0.0001$).

The hourly SBP variability according to 90-day outcomes (dichotomized into good functional outcome [mRS score 0–3] and death or disability [mRS score 4–6]) in 961 patients is presented in Fig. 2. The hourly SBP variability was higher in patients with death or disability compared with those with good functional outcome for the first eight hours after randomization. The SBP variability at 5 h ($P = 0.014$), 6 h ($P = 0.014$), and 13 h ($P = 0.04$) after enrollment was significantly associated with death or disability at 90 days, with positive but not statistically significant associations observed at all other points up to 8 h after randomization (see Fig. 2 and Supplemental Table S1). The proportions of patients with hematoma expansion (33.5% vs. 18.5%, $P < 0.001$), neurological deterioration (30.7% vs. 7.2%, $P < 0.001$), and AKI (8.7% vs. 3.7%, $P < 0.001$) were significantly higher among patients who experienced death or disability at 90 days (Table 1).

Risk of neurological deterioration within 24 h was highly associated with higher SBP variability, with the largest association observed between 1 ($P < 0.001$) and 5 h ($P < 0.001$) and prominent effects observed up to 22 h ($P = 0.03$) following randomization, significant associations observed up to 19 h following randomization, and trends observed up to 21 h following randomization (see Fig. 3 and Supplemental Table S2).

The risk of hematoma expansion within 24 h was associated with higher SBP variability between three ($P = 0.015$) and eight ($P = 0.002$) hours after randomization (see Fig. 4 and Supplemental Table S3).

Statistically significant associations between SBP variability and the risk of AKI were not observed. There was a trend toward association of maximum SBP being significantly associated with AKI between one and five hours after enrollment, with the value at two hours achieving statistical significance ($P = 0.026$) (see Fig. 5 and Supplemental Table S4).

There was no clear relationship between the magnitude of variability and its relationship with death or disability (see Table 1) or other outcomes (see Supplemental

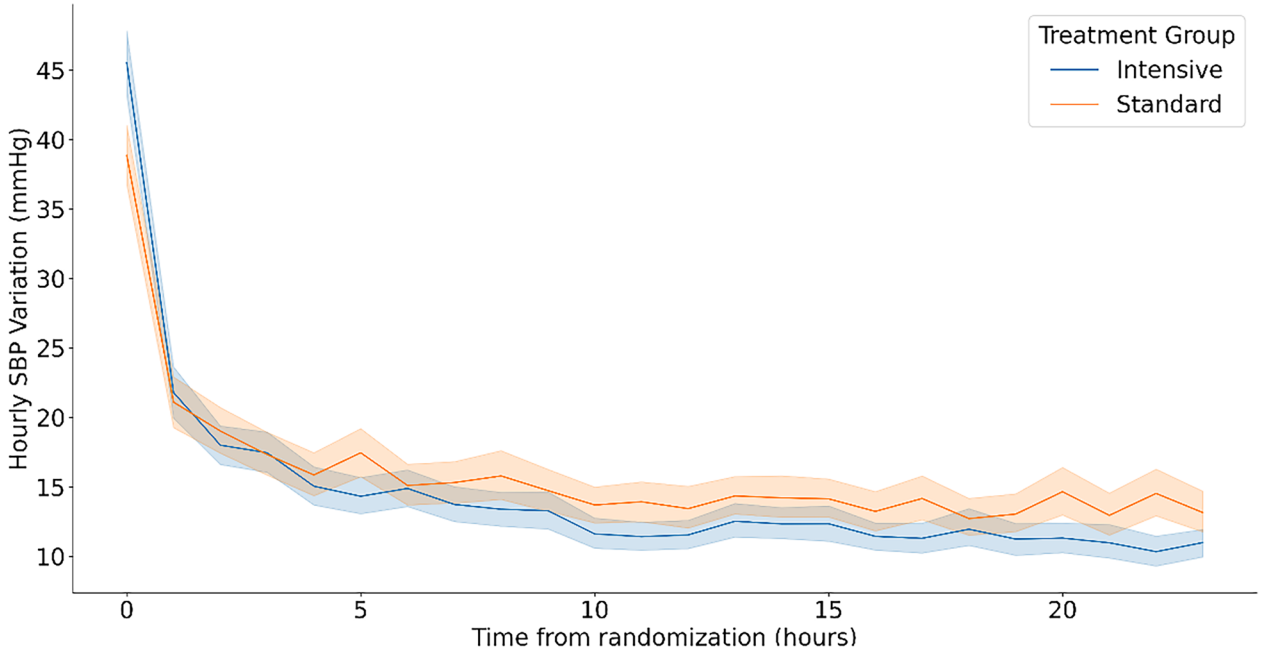

Fig. 1 Hourly systolic blood pressure (SBP) variability according to allocated treatment group

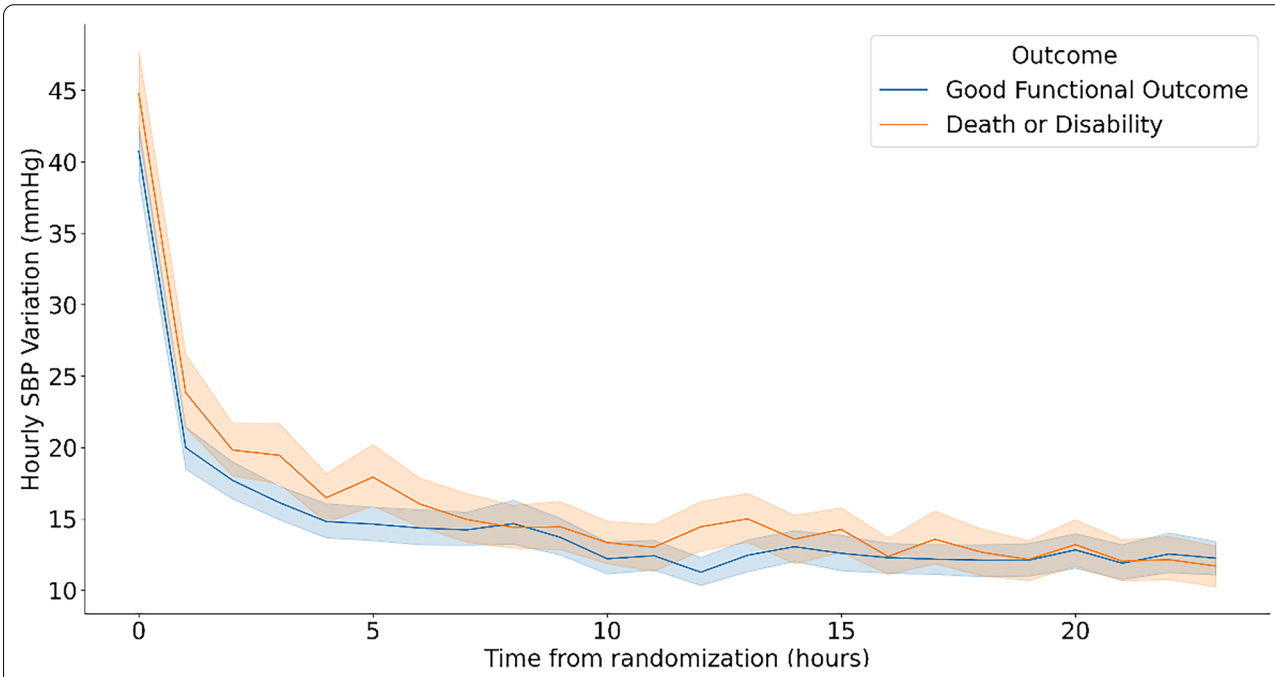

Fig. 2 Hourly systolic blood pressure (SBP) variability according to the 90 days after enrollment dichotomized into death or disability or good functional outcome

Tables S5, S6, S7). The largest effect was in hour 7, with the SBP variability magnitudes of the second quartile (5.0–12.0 mm Hg), third quartile (12.0–21.0 mm Hg), and fourth quartile (21.0–142.0 mm Hg) being associated with a higher risk of death or disability. The highest quartile at eight to ten hours had a significant relationship with neurological deterioration.

Table 1 Effect of magnitude of systolic blood pressure variability on good functional outcome expressed as *P* values

Hours[a]	1	2	3	4	5	6	7	8	9	10	11	12
Fourth[b]	0.13	0.97	0.80	0.75	0.71	0.81	0.04	0.54	0.53	0.50	0.55	0.70
Third[b]	0.61	0.48	0.29	0.13	0.34	0.84	0.02	0.03	0.84	0.09	0.58	0.05
Second[b]	0.66	0.78	0.35	0.32	0.37	0.38	0.02	0.31	0.19	0.89	0.81	0.29
First[b]	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Hours[a]	13	14	15	16	17	18	19	20	21	22	23	24
Fourth[b]	0.32	0.14	0.29	0.45	0.89	0.95	0.72	0.41	0.94	0.46	0.99	0.72
Third[b]	0.74	0.73	0.39	0.29	0.48	0.83	0.83	0.83	0.59	0.69	0.89	0.46
Second[b]	0.34	0.37	0.54	0.27	0.93	0.30	0.41	0.96	0.66	0.24	0.08	0.31
First[b]	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

Ref, reference

[a] Time in hours since randomization

[b] Quartiles defined by magnitude of systolic blood pressure change

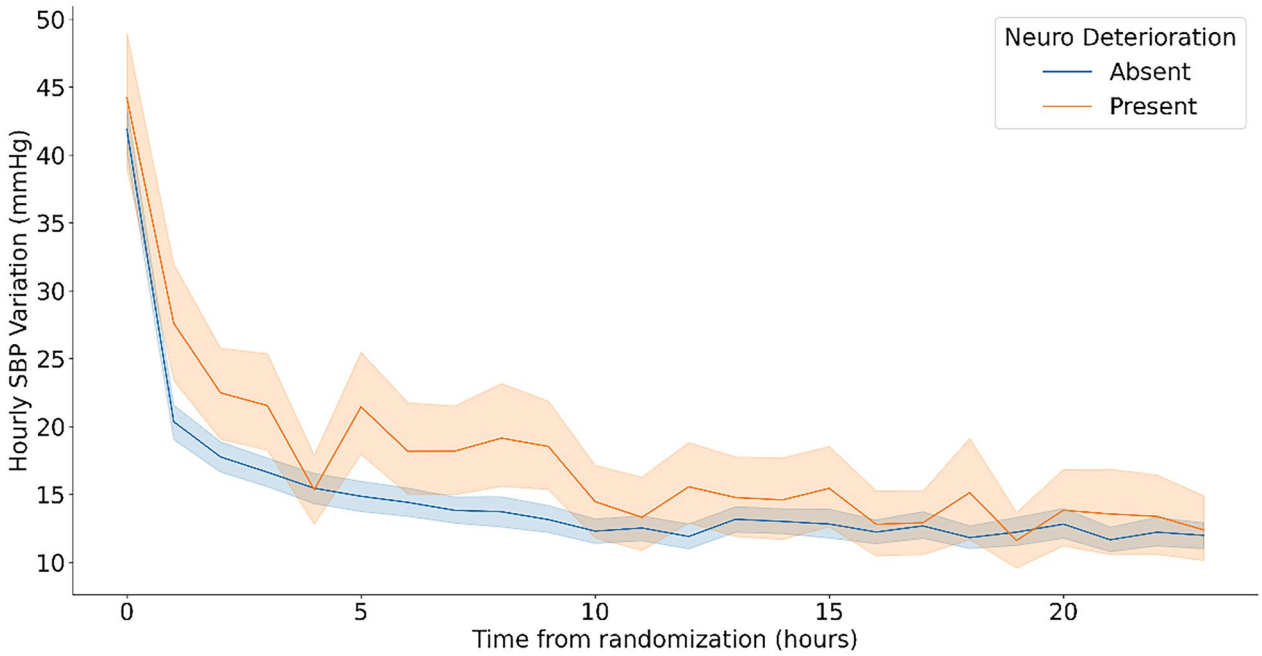

Fig. 3 Hourly systolic blood pressure (SBP) variability according to the occurrence of neurological deterioration within 24 h after randomization

Discussion

We observed a time-dependent effect of SBP variability on death or disability, with the most prominent relationship seen within the first eight hours after randomization, which achieved statistical significance 5 h, 6 h, and 13 h after randomization. The relationship between SBP variability and hematoma expansion was most prominent within eight hours after randomization. Risk of neurological deterioration within 24 h was highly associated with SBP variability, with the largest association observed between one and five hours following randomization, with significant associations observed up to 22 h following randomization. Various measures of SBP variability have been associated with death or disability after ICH [2, 3, 7, 8]. However, the data regarding the effect of SBP variability as a function of time are not well studied. We also found that SBP variability was higher in patients randomized to standard SBP reduction. The protocol required that IV nicardipine be discontinued if SBP was reduced to below 140 mm Hg, with an effort to create an SBP profile in patients randomized to a standard SBP reduction distinct from the one observed in patients randomized to an intensive SBP reduction. This was relatively frequent

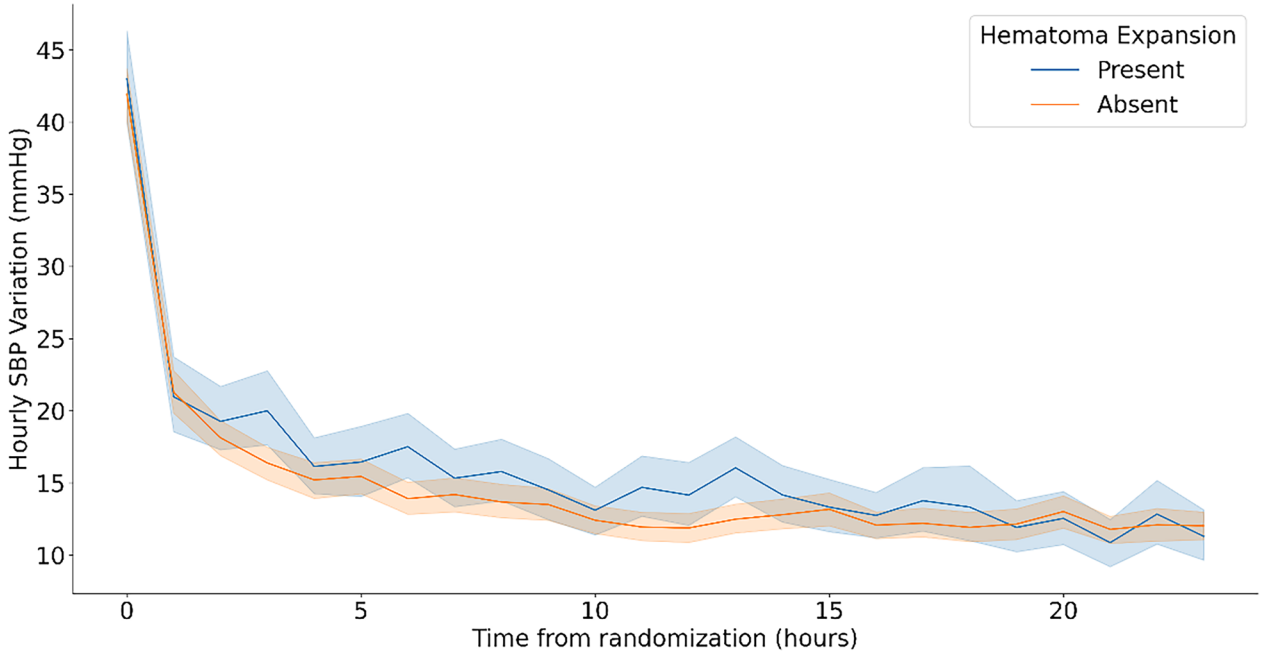

Fig. 4 Hourly systolic blood pressure (SBP) variability according to the occurrence of hematoma expansion within 24 h after randomization

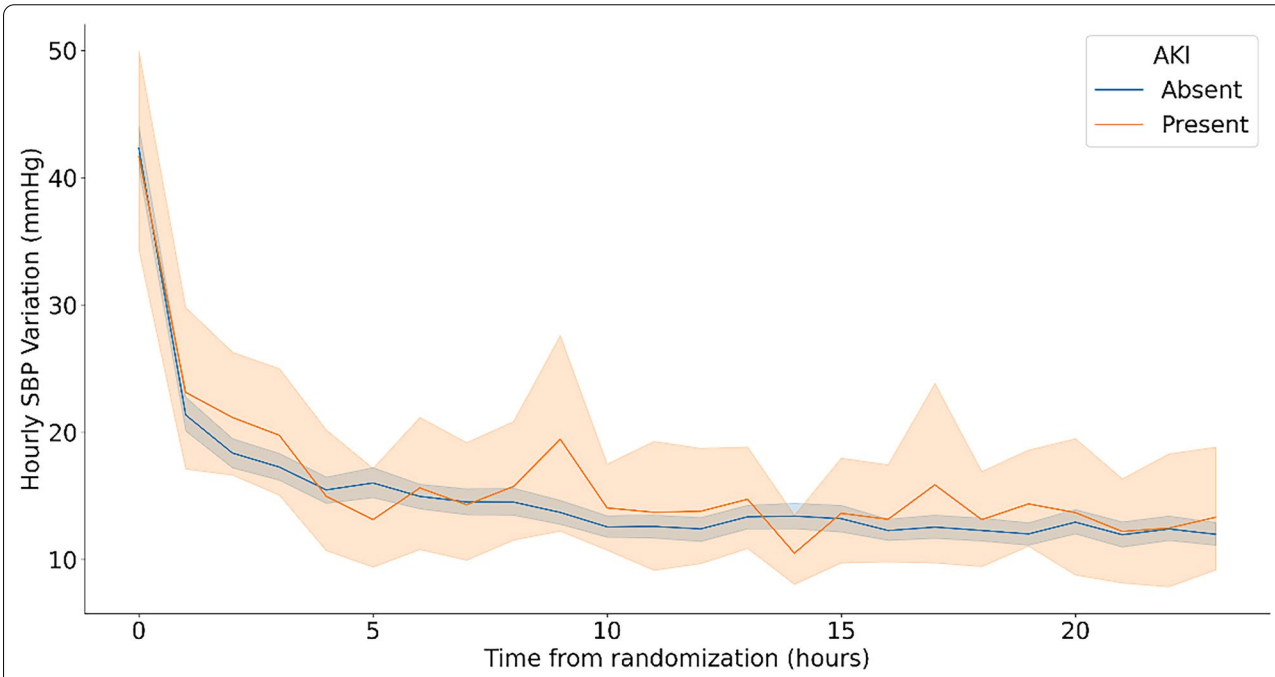

Fig. 5 Hourly systolic blood pressure (SBP) variability according to the occurrence of acute kidney injury (AKI) within 72 h after randomization

because of a combination of spontaneous SBP reduction and an escalating titration schedule of IV nicardipine. Abrupt and multiple discontinuations of IV nicardipine may have contributed to higher fluctuations in patients randomized to a standard SBP reduction.

The concept of a time window for a detrimental effect of SBP variability may be similar to the time-dependent effect of SBP reduction on hematoma expansion and death or disability [9–11]. The first 24 h after symptom onset have been identified as the time period when

higher SBP variability leads to higher rates of death or disability in patients with ICH in analyses of the FAST-MAG trial, SAMURAI-ICH study cohort, ATACH-2 trial, and INTERACT-2 and a pooled analysis of the INTERACT-2 and ATACH-2 trial [1–4]. Rodriguez-Luna et al. found that lower SD values of SBP and diastolic BP at various time intervals (0–2 h, 0–8 h, 0–12 h, 0–24 h, 0–48 h, and 0–72 h) were significantly associated with a good outcome [12]. The statistical significance of these associations strengthened over longer periods and was especially notable at 0–8 h (odds ratio 0.955, $P=0.001$). Mengel et al. reported that within the initial two-hour period after admission, patients with hematoma expansion exhibited a lower mean SBP (144.9 ± 23.6 mm Hg vs. 152.5 ± 21.2 mm Hg, $P=0.041$), with the same trend in the 0–8-h, 0–12-h, and 0–24-h time frames, without reaching statistical significance [13]. However, the measures of BP variability, successive variation, SD, and coefficient of variation were not significantly associated with hematoma expansion in any of the time windows studied.

The practical implications of these findings are predominantly focused on the duration of monitoring of SBP. The American Heart Association/American Stroke Association 2022 guidelines acknowledge that high SBP variability during the hyperacute and acute phases of ICH is associated with death or disability [14]. The guidelines recommend that any IV antihypertensive drug with rapid onset and short duration of action to facilitating easy titration and smooth and sustained BP control to minimize SBP variability (avoiding peaks and large variability) may be beneficial to improving functional outcomes [14]. The importance of the balance between rapid (within two hours of symptom onset) SBP reduction (magnitude of 55–85 mm Hg), which is associated with reduction in hematoma expansion and possibly better functional outcomes [10, 15], and the need to minimize SBP variability during the acute phase of ICH requires attention. A new therapeutic target—"systolic BP reduction with stability"—has been proposed to optimize the two competing needs in SBP treatment in patients with ICH, which requires SBP reduction to a value of 130–150 mm Hg and maintenance with two consecutive SBP recordings 15 min apart within the same range [16]. The Blood Pressure Variability in Cerebrovascular Emergencies Consortia proposed bifurcating SBP variability into two distinct periods—SBP variability$_1$ and SBP variability$_2$. SBP variability$_1$ involves hyperacute management, when rapid and smooth BP control is crucial. SBP variability$_2$, the plateauing phase, consists of a more gradual, maintenance-therapy slope [17].

It remains unclear whether SBP variability directly contributes to death or disability or is a manifestation of ongoing neurological injury after ICH, such as hematoma expansion or intracranial hypertension [13, 18–20]. The implications are different, as reducing SBP variability is only going to be beneficial if there is a causal relationship with neurological outcomes. In the absence of a causal relationship, an SBP variability reduction is unlikely to be beneficial. The question cannot be answered unless the effect of reducing SBP variability on various neurological outcomes is studied in patients with ICH. There is no conclusive evidence that a therapeutic intervention can reduce SBP variability. In a previous study, we studied pretreatment and post-treatment SBP-related variables in patients with acute stroke receiving IV clevidipine, nicardipine, or nitroprusside using data provided in the Medical Information Mart for Intensive Care (MIMIC)-IV database [8]. The mean SBP was significantly lower post-treatment compared with the pretreatment values for clevidipine (130.7 vs. 142.5, $P=0.006$), nicardipine (132.8 vs. 141.6, $P\leq0.001$), and nitroprusside (126.2 vs. 139.6, $P\leq0.001$). There were no differences in the mean post-treatment compared with the pretreatment values for clevidipine (14.5 vs. 13.5, $P=0.407$), nicardipine (14.2 vs. 14.6, $P=0.142$), and nitroprusside (14.8 vs. 14.8, $P=0.997$). IV antihypertensive medication reduced SBP but did not reduce SBP variability in this observational study. One strategy may be to reduce or ameliorate factors that increase SBP variability in patients with ICH [21]. The underlying mechanisms are not well understood [21] and include central sympathetic drive and arterial and cardiopulmonary reflexes, elastic properties (compliance) of the arteries, and changes in serum enzyme and peptide levels (angiotensin II, bradykinin, endothelin-1, insulin, nitric oxide). The overall SBP variability is probably related to complex interactions between the factors mentioned previously but without any clear therapeutic target [22, 23]. The ongoing Clevidipine for the Antihypertensive Treatment of Acute Intracerebral Hemorrhage (CLUTCH) trial (ClinicalTrials.gov identifier NCT06402968) targets SBP variability by using SBP reduction with stability as the primary end point ascertaining the time to reach the SBP target with stability (defined by the time interval between the initial SBP at the time of initiating IV clevidipine or alternate IV antihypertensive regimen and the first of the three consecutive recordings with SBP of < 150 mm Hg and > 130 mm Hg), consistent with principles of American Heart Association/American Stroke Association guidelines [14].

The exact frequency of SBP measurements that is necessary to identify prognostically important SBP variability is not clear. There is probably a difference between the frequency of SBP recordings that can be analyzed later to determine SBP variability and the frequency of SBP recordings that can be monitored in real time to guide IV antihypertensive medication titration. The ATACH-2

trial has recommended SBP measurements every 15 min in the first hour with higher frequency if required during a titration of IV nicardipine [5]. When using an IV antihypertensive medication with a shorter half-life, such as clevidipine, SBP measurements every five minutes may be optimal. However, nursing staff may not be able to respond (by adjusting dose of IV antihypertensive medication) to multiple SBP values obtained within five minutes [8]. Using artificial intelligence to process a higher frequency of SBP measurements and recommend dose changes is currently being explored [24].

Several factors need to be considered prior to interpretation of the results of our analysis. This is a post-hoc analysis of previously collected data as part of a randomized clinical trial [5]. The methodology of data collection was not optimized specifically for ascertainment of SBP variability [25]. The protocol required the collection of maximum and minimum SBP, recording for each hour in the first 24 h—thus effectively capturing the hourly range—but did not specify the maximum of number of SBP recordings per patient, which may vary between patients, introducing an unknown ascertainment bias. The trial protocol did not specify any adjustment in IV antihypertensive treatment to minimize the SBP variability but focused on maintaining SBP within the range specified by the allocated treatment (intensive or standard treatment). Our analysis cannot determine whether SBP variability was the cause or effect of certain end points, such as hematoma expansion and neurological deterioration. Similarly, an in-depth analysis of factors that may increase SBP variability was not possible. Our data do not provide any pathophysiological insights into the intracranial process occurring as a consequence of ICH within the first few hours that are affected by SBP variability [26]. There were other measures of SBP variability, such as SD, coefficient of variation, variation independent of mean, residual SD, average real variability, and successive variation [8], that were not studied in our analysis.

Reduced SBP variability within the first eight hours following randomization appears to be most impactful on both short-term and long-term outcomes in patients with ICH, and the first eight hours may represent a time window for future interventions directed at reducing SBP variability in patients with ICH.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s12028-025-02376-0.

Author details
[1] Zeenat Qureshi Stroke Institute, Columbia, MO, USA. [2] University of Missouri, Columbia, MO, USA. [3] Institute for Data Science and Informatics, University of Missouri, Columbia, MO, USA. [4] Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA. [5] Mayo Clinic, Rochester, MN, USA. [6] University of South Florida Morsani College of Medicine/Tampa General Hospital, Tampa, FL, USA. [7] Division of Neurosciences Critical Care, The Johns Hopkins School of Medicine, Johns Hopkins University, Baltimore, MD, USA. [8] Varisano Klinikum Frankfurt Höchst, Frankfurt, Germany. [9] University of Heidelberg, Heidelberg, Germany.

Author contributions
A.I.Q., J.A.G., and C.-R.S. contributed to conceptualization and design of the study. A.I.Q., W.B., P.L., A.A.R., D.Z.R., J.I.S., and T.S. contributed to data collection and processing. W.B., J.A.G., and C.-R.S. performed data analysis and interpretation. A.I.Q., W.B., and P.L. drafted the manuscript. J.A.G., A.A.R., D.Z.R., J.I.S., T.S., and C.-R.S. performed critical review of the manuscript. A.I.Q. and J.A.G. supervised and provided oversight. All authors approve the final version of the manuscript.

Declarations

Conflicts of interest
None.

Ethical approval
We confirm adherence to ethical guidelines; for the ATACH-2 trial, ethical approvals (institutional review board) and informed consent were used.

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Received: 23 March 2025 Accepted: 26 August 2025
Published online: 24 September 2025

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